REMARKS

Claims 1-25 are pending. Claims 2 and 3 stand withdrawn from consideration as being directed to nonelected subject matter. Claims 4, 11, 12, 23, and 24 are cancelled without prejudice, and claims 26 and 27 have been added. Claims 1, 5-10, 13-22, and 25-27 will therefore be pending upon entry of the proposed amendments.

Applicants have amended claim 1 as follows. Applicants have deleted nonelected subject matter as required by the Examiner. Applicants have also deleted "prodrug moiety" from the definition of R_3. Finally, Applicants have amended the final clause of claim 1 to read "or a pharmaceutically acceptable salt, geometrical isomer, tautomer, optical isomer, or *N*-oxide form thereof" instead of "and pharmaceutically acceptable salt, hydrate, geometrical isomer, tautomer, optical isomer, *N*-oxide or prodrug form thereof." The final clause of claim 1 no longer recites the terms "prodrug" or "hydrate."

Applicants have amended claim 9 as follows. Applicants have amended the phrase "and their pharmacologically acceptable salts and solvates" in claim 9 to read "or a pharmacologically acceptable salt thereof." Applicants have also inserted the conjunction "and" between the second and third recited species.

Applicants have amended each of claims 13-21 to depend from claim 1 instead of claim 11 (now cancelled). Claims 13-21 as currently amended now include the limitations recited in claim 11.

Support for the amendments to claim 22 can be found throughout the Specification, e.g., at page 16, line 1 through page 21, line 13.

Support for new claims 26 and 27 can be found throughout the Specification, e.g., at page 16, lines 18-20.

No new matter is introduced by these amendments.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1 and 4-25 are rejected under 35 U.S.C. § 112, second paragraph on various grounds, each of which is addressed individually in the discussion below.

The rejection of claims 4, 11, 12, 23, and 24 are moot in view of their cancellation.

Claim 1

Claim 1 is rejected because the phrase "and pharmaceutically acceptable salt, hydrate...thereof" (Office Action, page 3) is allegedly indefinite. This rejection is moot in view of the amendments to claim 1.

Claim 1 is rejected because it recites "proviso (ii)" (Office Action, page 3). This rejection is moot in view of the amendments to claim 1.

Claim 1 is rejected because it "recites a prodrug thereof at two places which is confusing and unclear" (Office Action, page 3). This rejection is moot in view of the amendments to claim 1.

Claim 1 is rejected because recitation of the term "nitrogen protecting group" in the definition of variable R_3 allegedly renders claim 1 indefinite. The Office has argued (Office Action, page 3):

> [R] ecitation of N-protecting group in the definition of R_3 renders the claim indefinite as it is not clear what is a metes and bounds of the claim1. A nitrogen protecting group can be any number of groups with varying structural features and there is no evidence that they all will have the same intended use.

Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

As will be discussed in more detail below, a claim when read in conjunction with the Specification, must **reasonably** apprise the **skilled artisan** of its boundaries to the extent that the claimed subject matter permits. Protecting groups in general, including nitrogen protecting groups, and their intended use were known (arguably were well known) in the art of organic chemistry as of Applicants' filing date. Thus, a person of ordinary skill in the art reading the present claims in conjunction with the Specification (which discloses both the specific structure of the substrate to be protected as well as the chemical reactions that the substrate is exposed to) would understand the metes and bounds of the limitation "a nitrogen protecting group."

Legal Standards for Definiteness

The Federal Circuit discussed the statutory requirements of 35 U.S.C. § 112, ¶2 in *S3 Inc. v. nVIDIA Corp.* 59 USPQ2d 1745, 1747, (2001):

> The requirement that the claims 'particularly point[] out and distinctly claim[]' the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification. 'If the claims when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more' *[citations omitted]*.

See also Hybritech Inc. v. Monoclonal Antibodies, Inc. 231 USPQ 81, 94 (Fed. Cir. 1986) ("'if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more,' quoting *Shatterproof Glass Corp. v. Libbey Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985); *In re Warmerdam* 31 USPQ2d 1754, 1759 (Fed. Cir. 1994) ("The legal standard for definiteness is whether a claim reasonably apprises those of skill in the art of its scope).

Protecting Groups

Protecting groups, and their use, are known in the art. A protecting group in organic chemistry refers to a moiety, which when attached to a potentially reactive site (e.g., a functional group, e.g., an amino group), temporarily blocks that reactive site so as to render it chemically inert. A prior art treatise on protecting groups provides as much:

> When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been, and are being developed for this purpose (T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley and Sons (1981), page 1).

Thus, a reactive site may be blocked, e.g., during the course of the synthesis of an organic molecule, because it is incompatible with a synthetic operation involving a different reactive site on a starting material (e.g., incompatibility can mean that the reactive site to be blocked is degraded by, or, as indicated in the above passage from Greene, would interfere with the reagents or reaction conditions associated with the synthetic operation involving the different reactive site). A corollary property of protecting groups is that they can be introduced and removed (i.e., "deprotected") without complete destruction of the starting material and subsequent reaction product, respectively. Finally, many candidate protecting groups for a variety of functional groups, including amino groups, were known as of Applicants' filing date (see, e.g., the Greene reference cited above).

One of ordinary skill in the art, when reading the present claims in conjunction with the Specification, knows the meaning of the term "a nitrogen protecting group"

The Office asserts "there is no evidence that they [*sic.* nitrogen protecting groups] all will have the same intended use." (Office Action, page 3).

While the selection of a protecting group may vary from reaction to reaction and substrate to substrate, the skilled artisan would understand that the intended use of any protecting

group is to block a reactive site that is incompatible with a synthetic operation involving a different reactive site on a starting material should. Further, the skilled artisan would understand that any protecting group should be, in general, sufficiently stable to block (i.e., protect) the reactive site for the entirety of the synthetic operation yet sufficiently labile to permit regeneration of the protected reactive site without complete destruction of the substrate. This is true regardless of whether the protecting group is employed to protect a functional group from acidic conditions, basic conditions, oxidative conditions, and so forth. It follows that a person of ordinary skill in the art, knowing the nature of the synthetic operation and the structure of the substrate (both of which are provided in the Specification), would be able to determine what would and would not be a suitable protecting group for a given reactive site on that substrate.

In other words, a person of ordinary skill in the art reading the present claims in conjunction with the Specification would understand both the meaning and metes and bounds of the term "a nitrogen protecting group" because at the very least (1) the existence, synthesis, use, and operative scope of "protecting groups," which are what is attached to a functional group when it is "protected," were known in the art as of Applicants' filing date; and (2) the Specification not only provides a listing of exemplary protecting groups (see, e.g., page 20, lines 1-2), but also delineates in both a general and specific manner, the chemical reactions to which the claimed protected compounds would be subjected to and need to be protected from; and (3) many candidate protecting groups for a variety of functional groups, including nitrogen protecting groups, were known as of Applicants' filing date. In short, protecting groups, in particular nitrogen protecting groups, were known (and arguably well known) as of Applicants' filing date.

The term "a nitrogen protecting group," as used in the present claims, does indeed cover many known nitrogen protecting groups. However, mere fact that a claim term has breadth (which is justified and supported in the present case), does not render that term indefinite. *See Union Pacific Resources Co. v. Chesapeake Energy Corp.* 57 USPQ2d 1293, 1297 (Fed. Cir. 2001) ('Breadth is not to be equated with indefiniteness...' quoting *In re Miller* 441 F.2d 689, 693, 169 USPQ 597, 600 (CCPA 1971)).

In summary, a definite claim is a claim that apprises one of ordinary skill in the art of its scope and serves notice to others as to what constitutes infringement of the patent (MPEP 2173.02). The present claims certainly provide this public notice function because guided by his or her skill in the art and/or the Specification (which provides substrate structure and delineates reaction conditions that must be tolerated by the substrate), a person of ordinary skill in the art would understand the metes and bounds of a "a nitrogen protecting group." Moreover, the degree of specificity of "a nitrogen protecting group" (as well as all of the limitations recited in the present claims) meets the legal standards for definiteness set forth in the relevant case law discussed above. As such, the present claims are fully compliant with 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 9

Claim 9 is rejected because "it appears to be missing a an 'and' before the third species and for reciting 'and their pharmacologically acceptable salts and solvates thereof'" (Office Action, page 3). This rejection is moot in view of the amendments to claim 9.

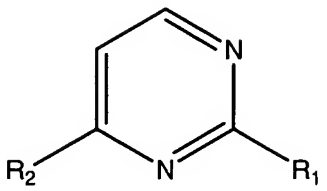
Claim 22

Claim 22 is rejected for allegedly "omitting essential steps" (Office Action, page 4). The Office has argued (Office Action, page 4):

> Claim 22 is rejected under 35 U.S.C., second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP 2172.01. The omitted steps are: the actual reactants are omitted rendering the claim a cryptic claim. Not reacting with chemical reagents wouldn't lead to a desired product.

The rejection has been met, in part, by amending the claims. These amendments are discussed in more detail below.

The present claims are directed to various 2,4-disubstituted pyrimidinyl compounds having general formula (**A**):

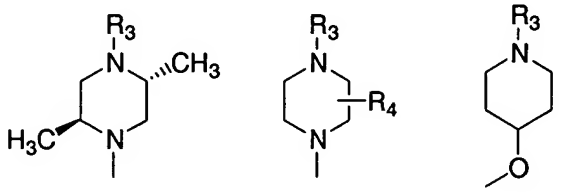


(A)

and to methods of making and using the claimed compounds.

Substituents R_1 and R_2 are defined in claim 1 as follows (emphasis added):

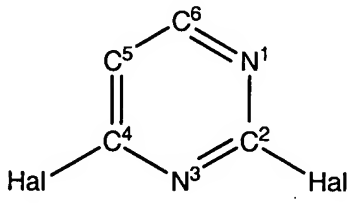
"R_1 and R_2 are each, independently, selected from a **group A** consisting of:



or from a **group B**, consisting of aryl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkoxy, aryloxy-C_2-C_6-alkoxy, heteroaryloxy-C_2-C_6-alkoxy, 1-indanyloxy, 2-indanyloxy, aryloxy, heteroaryloxy, arylthio, heteroarylthio, C_5-C_6-cycloalkylthio, C_5-C_8-alkoxy, C_5-C_8-alkylthio, C_3-C_6-alkynyloxy, C_3-C_6-alkenyloxy, fluoro-C_2-C_4-alkoxy, C_4-C_8-cycloalkyloxy, C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, halogen, aryl-C_1-C_4-alkylthio, heteroaryl-C_1-C_4-alkylthio, aryl-C_1-C_4-alkylamino, heteroaryl-C_1-C_4-alkylamino, heteroaryl and aryl;"

The claim further requires, *inter alia*, that (i) R_1 and R_2 must be different from one another; and (ii) R_1 and R_2 cannot both be selected from group A or from group B (i.e., one of R_1 and R_2 must be selected from group A, and the other must be selected from group B).

The Specification teaches that the claimed compounds (as well as other compounds embraced by claim 1 as originally filed) can be prepared from a 2,4-dihalopyrimidine starting material of formula (**B**) (see Specification, e.g., at page 16, line 16 through page 21, line 15):

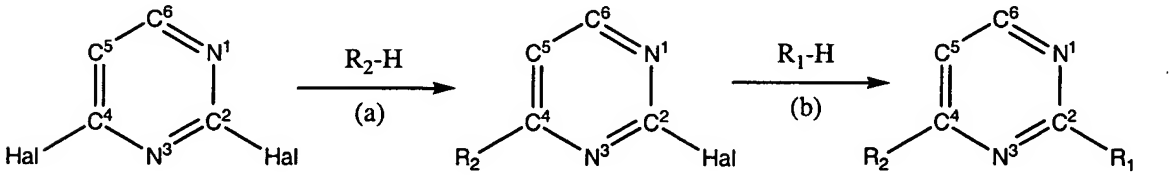


(B)

Each of the pyrimidine ring atoms in formula (**B**) is numbered according to convention, and each "Hal" in formula (**B**) represents a halogen.

The two halogens in formula (B) can be substituted, in a stepwise manner, by one group A substituent and by one group B substituent (or *vice versa*). Typically, the first substitution occurs at C-4 of the pyrimidine ring, and the second substitution occurs at C-2 of the pyrimidine ring. The overall process is summarized in Scheme 1 below:

Scheme 1

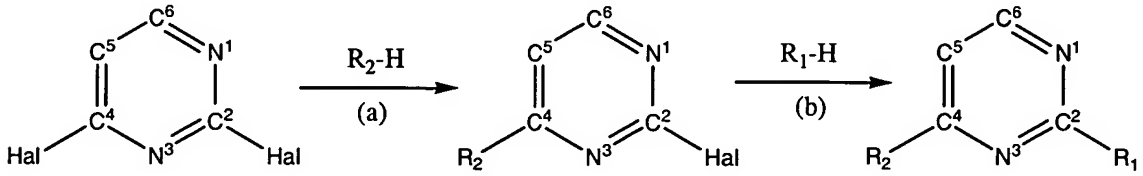


"R_2-H" in step (a) is a reagent for introducing substituent R_2 in formula (I), and "R_1-H" in step (b) is a reagent for introducing substituent R_1 in formula (I). Such reagents can include, e.g., alcohols, amines, thiols, and aryl/heteroaryl boronic acids.

The Specification goes on to disclose that the foregoing process can provide compounds in which R_2 (attached to C-4 of the pyrimidine ring) is a group B substituent, and R_1 (attached to

C-2 of the pyrimidine ring) is a group A substituent as well as compounds in which R_2 is a group A substituent, and R_1 is a group B substituent (as discussed elsewhere, the claims require that one of R_1 and R_2 must be selected from group A, and the other must be selected from group B).

For example, compounds in which R_2 is a group B substituent and R_1 is a group A substituent can be prepared according to Scheme 1 as follows:

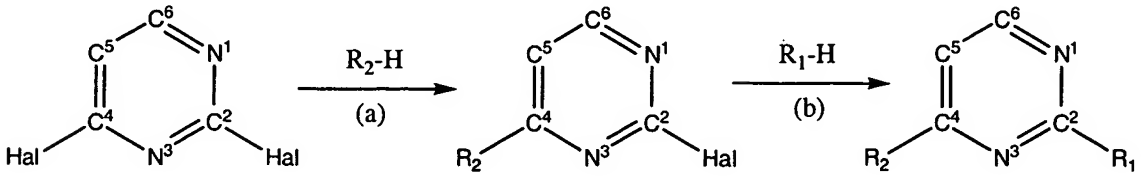


R_2 in R_2-H is a **group B** substituent

R_1 in R_1-H is a **group A** substituent

in which a reagent that can introduce a group B substituent is employed in step (a) of Scheme 1; and a reagent for introducing a group A substituent is employed in step (b) of Scheme 1. See, e.g., methods "A," "B," and "D" in the Specification at page 17, line 18 through page 20, line 4 and page 21, line 10 through page 22, line 5.

Conversely, compounds in which R_2 is a group A substituent and R_1 is a group B substituent can be prepared according to Scheme 1 as follows:



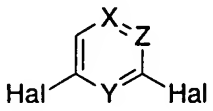
R_2 in R_2-H is a **group A** substituent

R_1 in R_1-H is a **group B** substituent

in which a reagent that can introduce a group A substituent is employed in step (a) of Scheme 1; and a reagent for introducing a group B substituent is employed in step (b) of Scheme 1. See, e.g., methods "C" and "E" in the Specification at page 20, line 6 through page 21, line 8 and page 22, lines 7-10.

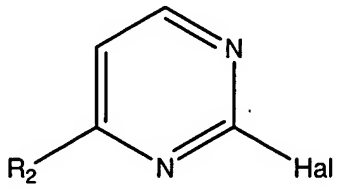
Thus, to further clarify the nature of the steps in claim 22, Applicants have amended claim 22 to include the following steps:

(a) converting a compound of the following formula:



wherein Y and Z represent both nitrogen and X represents CH, forming a pyrimidine derivative, and wherein each Hal is independently a halogen;

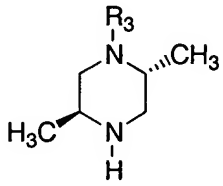
to a compound of formula (IX):

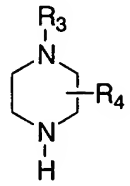


(IX)

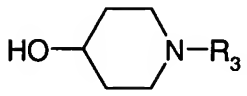
in which R_2 is a group B substituent; and

(b) contacting the compound of formula (IX) with a compound selected from the group consisting of:





and

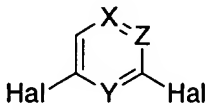


(XI)

(i.e., contacting the formula (IX) compound with a reagent for introducing one of the three permissible group A substituents);

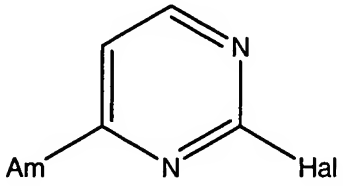
OR

(a') converting a compound of the following formula:



wherein Y and Z represent both nitrogen and X represents CH, forming a pyrimidine derivative, and wherein each Hal is independently a halogen;

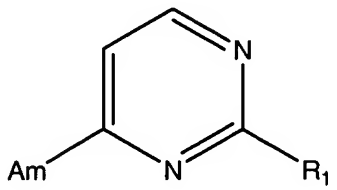
to a compound of formula (XIII):



(XIII)

in which "Am" is a group A substituent; and

(b') converting the compound of formula (XIII) to a compound of the formula:



in which R_1 is a group B substituent.

In view of the foregoing, Applicants submit that claim 22 as currently amended does not omit matter disclosed to be essential to the claimed methods of preparing the compounds of claim 1.

Claim 25

Claim 25 is rejected because because it allegedly "lacks antecedent basis in claim 1" (Office Action, page 4).

Applicants respectfully disagree. Claim 25 is directed to compounds in which "R_3 is an acyl- or alkoxycarbonyl group forming a cleavable amide or carbamate linkage." Amino groups can be protected as amides or carbamates by attaching to the nitrogen atom of the amino group an acyl nitrogen protecting group or an alkoxycarbonyl nitrogen protecting group, respectively (see, e.g., T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley and Sons (1981)). The definition of R_3 in claim 1 recites "a nitrogen protecting group" as one of the permissible substituents for R_3. As such, the recitation of "a nitrogen protecting group" in the definition of R_3 in claim 1 provides antecedent basis for the limitations recited in claim 25, which depends from claim 1. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1 and 4-25 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. The Office has argued that the Specification "does not reasonably provide enablement for making prodrug" or "solvate or hydrate" forms of the claimed compounds (Office Action, pages 4 and 7).

The rejection of claims 4, 11, 12, 23, and 24 are moot in view of their cancellation.

Applicants respectfully disagree with the grounds for the rejection, however, to expedite prosecution, Applicants have deleted both occurrences of "prodrug" in claim 1, "hydrate" from claim 1, and "solvate" from claim 9. Applicants respectfully request reconsideration and withdrawal of the rejection in view of the foregoing amendments to claims 1 and 9.

Claims 11-13, 15-21, and 23-24 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. The Office has argued (Office Action, page 11):

> [T]he specification, while being enabling for treatment of obesity embraced, does not reasonably provide enablement for prophylaxis of any or all diseases and disorder embraced in the claim language.

The rejection of claims 11, 12, 23, and 24 are moot in view of their cancellation.

Applicants respectfully disagree with the grounds for the rejection, however, to expedite prosecution, claims 13-21 as currently amended are directed to methods for treatment only of eating disorders; obesity; memory disorders; mood disorders; anxiety disorders; sexual dysfunctions, epilepsy, or urinary disorders; pain; substance abuse; and schizophrenia, respectively (sexual dysfunctions, epilepsy, or urinary disorders are recited together and in the alternative in claim 18).

Applicants submit with this Reply a Supplemental Information Disclosure Statement to disclose articles that describe the involvement of 5-HT2c in various disorders. See, e.g.:

Pain

Chojnacka-Wojcik E, Klodzinska A, Deren-Wesolek A. *Pol J Pharmacol.* **1994** Sep-Oct;*46*(5):423-8. "Involvement of 5-HT2C receptors in the m-CPP-induced antinociception in

mice." ("Intraperitoneal administration of m-CPP (1-10 mg/kg) produced a dose-dependent antinociception in both those tests; the effect of m-CPP in the hot plate test was stronger. The antinociceptive effect of m-CPP in either test was abolished by pretreatment with mesulergine (2 mg/kg), ritanserin (1-2 mg/kg), 5-HT2A/5-HT2C receptor antagonists, and metergoline (0.5-2 mg/kg), a non-selective 5-HT receptor antagonist. On the other hand, spiperone (0.25-0.5 mg/kg), a dopamine, 5-HT1A and 5-HT2A receptor antagonist; pindolol (4-8 mg/kg), a beta-adrenoceptor, 5-HT1A and 5-HT1B receptor antagonist and zacopride (0.1-1 mg/kg) a 5-HT3 receptor antagonist, did not affect the analgesia induced by m-CPP. Neither of the drugs used as putative receptor antagonists changed the nociceptive responsiveness in mice. The obtained results suggest that the analgesia induced by m-CPP is mediated by 5-HT2C receptors." --see Abstract).

Mood disorders (e.g., depression)

Moreau, J.-L.; Boes, M.; Jenck, F.; Martin, J. R.; Mortas, P.; Wichmann, J. *European Neuropsychopharmacology* **1996** *6*(3), 169-175. "5HT2C receptor agonists exhibit antidepressant-like properties in the anhedonia model of depression in rats." ("In stressed animals, chronic treatment with the preferential 5HT2C receptor agonists Ro 60-0175 and Ro 60-0332 (3 mg/kg i.p. b.i.d.) prevented the loss of sensitivity to reward. Similarly, when stressed anhedonic animals were curatively treated with Ro 60-0175 (3 mg/kg i.p. b.i.d.), the stress-induced anhedonia was gradually reversed. These results suggest a role for 5HT2C receptors in some aspects of depression, and potential antidepressant properties for selective 5HT2C receptor agonists. Such compds. may offer an innovative approach to the treatment of mood disorders" --see Abstract).

Cryan JF, Lucki I *J Pharmacol Exp Ther.* **2000** Dec;*295*(3):1120-6. "Antidepressant-like behavioral effects mediated by 5-Hydroxytryptamine(2C) receptors." ("Three novel selective 5-HT(2C) receptor agonists, WAY 161503 (0.1-3.0 mg/kg), RO 60-0175 (2-20 mg/kg), and RO 60-0332 (20 mg/kg), all decreased immobility and increased swimming, a pattern of behavior similar to that which occurs with the selective serotonin reuptake inhibitor fluoxetine

(5-20 mg/kg). However, the prototypical but nonselective 5-HT(2C) receptor agonist m-chlorophenylpiperazine (1-10 mg/kg) increased immobility scores in the forced swim test. The selective 5-HT(2C) receptor antagonist SB 206533 was inactive when given alone (1-20 mg/kg). However, SB 206533 (20 mg/kg) blocked the antidepressant-like effects of both WAY 161503 (1 mg/kg) and fluoxetine (20 mg/kg). The atypical antidepressant (noradrenergic alpha(2) and 5-HT(2C) receptor antagonist) mianserin reduced immobility and increased climbing at 30 mg/kg. At a behaviorally subactive dose (10 mg/kg), mianserin abolished the effects of WAY 161503 (1 mg/kg) on both swimming and immobility scores. Mianserin blocked the effects of fluoxetine (20 mg/kg) on swimming only; mianserin plus fluoxetine reduced immobility and induced a switch to climbing behavior, suggesting activation of noradrenergic transmission. These data exemplify the benefits of using the modified rat forced swim test, which was sensitive to serotonergic compounds and distinguished behavioral changes associated with serotonergic and noradrenergic effects. Taken together, the results strongly implicate a role for 5-HT(2C) receptors in the behavioral effects of antidepressant drugs." --see Abstract).

Schizophrenia

Piesla MJ, Comery TA, Brennan JA, Welmaker GS, Rosenzweig-Lipson S, Marquis KL. *Schizophrenia Res.* 49 (1-2): 95-95 Sp. Iss. SI Suppl. S, APR 15, **2001**. "Atypical antipsychotic-like effects of 5-HT2C agonists." ("These results, coupled with the absence of catalepsy in mice, suggest that 5-HT2C agonists show atypical antipsychotic-like effects" --see Abstract)

Substanse abuse

Grottick AJ, Fletcher PJ, Higgins GA. *J Pharmacol Exp Ther.* **2000** Dec;*295*(3):1183-91. "Studies to investigate the role of 5-HT(2C) receptors on cocaine- and food-maintained behavior." ("The present series of studies were designed to investigate the 5-HT(2C) receptor agonist Ro 60-0175 on cocaine- and food-maintained behavior in the rat. Ro 60-0175 (0.1-3 mg/kg, s.c.) reduced cocaine (15 mg/kg, i.p.)-induced hyperactivity. This inhibitory effect of Ro 60-0175 (1 mg/kg, s.c.) was completely blocked by pretreatment with the selective 5-HT(2C)

antagonist SB 242,084 (0.5 mg/kg, i.p.). In further studies, Ro 60-0175 (1-3 mg/kg, s.c.) reduced responding for both food (45-mg Noyes pellet) and cocaine (0.25 mg/infusion) maintained under identical schedules of reinforcement (fixed ratio (5), time out 1 min, 60-min duration). The effect on food-maintained responding was blocked by SB 242,084 (0.5 mg/kg, i.p.). Ro 60-0175 (0.3-3 mg/kg, s.c.) also reduced the breakpoint for cocaine self-administration under a progressive ratio schedule of reinforcement. After a period of extinction training, where cocaine solution was substituted with saline, an acute priming injection of cocaine (15 mg/kg, i.p.) but not Ro 60-0175 (1 mg/kg, s.c.) reinstated cocaine responding. In this model of relapse, Ro 60-0175 (1-3 mg/kg, s.c.) pretreatment attenuated the priming effect of acute cocaine injection. In a final series of studies to examine the cataleptogenic properties of Ro 60-0175, very mild indices of catalepsy were observed at the 3 mg/kg dose only. These catalepsy scores were significantly lower than that produced by haloperidol (0. 5 mg/kg, s.c.). In further tests of motor function using the Rotarod, deficits were again seen at the 3 mg/kg dose, but not at lower doses. Taken together, these studies suggest that, in addition to reducing food intake, 5-HT(2C) receptor agonists reduce cocaine-reinforced behavior. This would be consistent with electrophysiological and biochemical evidence suggesting an important modulatory influence of 5-HT(2C) receptor activation on mesolimbic dopamine function." --see Abstract).

Grottick AJ, Corrigall WA, Higgins GA. *Psychopharmacology* (Berl). **2001** Sep;157(3):292-8. "Activation of 5-HT(2C) receptors reduces the locomotor and rewarding effects of nicotine." ("Ro 60-0175 (0.3-3 mg/kg SC) dose-dependently reduced nicotine-induced activity, an effect which was reversed by SB 242,084 (0.5 mg/kg IP), thus confirming receptor selectivity of the response. Responding both for food and nicotine on an FR5TO1 min schedule of reinforcement was reduced by Ro 60-0175 (0.1-1 mg/kg) with proportionally similar effects on responses for both types of reinforcer. Co-administration of Ro 60-0175 (1 mg/kg SC) and nicotine (0.4 mg/kg SC) for 10 days blocked the sensitised response that developed in subjects treated with nicotine alone. CONCLUSIONS: The present data support an involvement for the 5-HT(2C) receptor in mediating mesolimbic DA functioning as assessed by changes in behaviours indicative of nicotine reward." --see Abstract).

Urinary disorders

Steers et al. ("Effects of serotonergic agonists on micturition and sexual function in the rat" *Drug Development Research* 1992, *27*(4), 361-75) report that: "5-HT1C/2 agonists abolished reflexly evoked bladder contractions by inhibiting efferent firing in the pelvic nerve. 5-HT1C/2 agonists also produced penile erections (2-5/30 min) via firing in cavernous nerves mediated by preganglionics in the pelvic nerve. Neural activity in the cavernous nerves following administration of MK212 and TFMPP was abolished by the 5-HT1C/2 antagonist mianserin. 5-HT1A, 5-HT1B, 5-HT1C/2 agonists failed to influence synaptic transmission in the pelvic ganglion. These data support a functional diversity of 5-HT receptor subtypes with selective excitation or inhibition of central-autonomic pathways regulating pelvic visceral function. These observations suggest that 5-HT1C/2 agonists could be clin. useful for managing impotence or urinary incontinence." Note: Prior to 1993, the 5-HT2C receptor was denoted 5-HT1C.

de Groat, ("Influence of central serotoneric mechanisms on lower urinary tract function. *Urology* 2002, *59 (Suppl. 5A)*, 30-36) reports that: "Although there is some evidence in the rate for serotonergic facilitation of voiding, most experiments in rats and cats indicate that activation of the central serotonergic system by 5-HT reuptake inhibitors, as well as by 5-HT_{1A} and 5-HT2 receptor agonists, depresses reflex blander contraction and increases the bladder volume threshold for inducing micturation ... The 5-HT receptors and reuptake mechanisms, therefore, represent targets for the development of new treatments of detrusor overactivity and urinary incontinence."

Steers et al. (Effects of *m*-chlorophenylpiperazine on penile and bladder function in rats. *Am. J. Physiol.* 1989, *257*, R1441-R1449) report that: "MCCP [a serotonin agonist] ...elicited, after a 2- to 4-min delay, an increase in spontaneous firing in cavernous nerves but no detectable firing in bladder nerves. The cavernous nerve firing was accompanied by an increase in intracavernous pressure and a depression of rhythmic bladder activity."

Guarneri et al. (The effects of *m*-CPP on bladder voiding contractions in rats are mediated by the 5-HT_{2A}/5-HT_{2C} receptors. *Neurourol. Urodyn.* 1996, *15*, 316-317) report that

the inhibitory effect of *m*-CPP on the bladder-voiding contractions in anaesthetized rats could be completely reversed by mesulergine (a 5-HT_{2C}/5-HT_{2A} antagonist). However, the *m*-CPP-induced inhibition of bladder-voiding contractions was potentiated following pretreatment with the 5-HT_{2A} antagonist ketanserin.

Testa et al. (Effect of different 5-hydroxytryptamine receptor subtype antagonists on the micturition reflex in rats. *BJU Int.* 2001, *87*, 256-264) report that that the selective 5-HT_{2C} receptor antagonist SB 242084 shows a tendency to increase the frequency of bladder contractions in rats. Thus, it appears that 5-HT_{2C} receptor antagonists could induce a state similar to overactive bladder.

Epilepsy

Mutant mice lacking the 5-HT_{2C} receptor appear to be more susceptible to seizures than wild-type controls, showing lower seizure thresholds and increased focal seizure excitability (Isaac "The 5-HT_{2C} receptor as a potential therapeutic target for the design of antiobesity and antiepileptic drugs." *Drugs Future* 2001, 26, 383-393; Tecott et al. "Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors." *Nature* 1995, *374*, 542-546; Applegate et al. "Global increases in seizure susceptibility in mice lacking 5-HT_{2C} receptors: A behavioural analysis. *Exp. Neurol.* 1998, *154*, 522-530; and Heisler et al. "Epilepsy and obesity in serotonin 5-HT_{2C} receptor mutant mice." *Ann NY Acad Sci* 1998, *861*, 74-78). The preferential 5-HT_{2C} receptor agonist *m*-CPP protects against pentetrazole-induced myoclonic and/or tonic seizures in mice and rats, and this effect was inhibited by the 5-$HT_{2C/2B}$ receptor antagonist SB-206553, whereas the 5-HT_{2B} receptor agonist BW-723C86 had no effect on the seizure threshold in these rodent models. This suggests that the anticonvulsant effect of *m*-CPP is 5-HT_{2C} receptor-mediated (Upton et al. "Studies on the role of 5-HT_{2C} and 5-HT_{2B} receptors in regulating generalized seizure threshold in rodents. *Eur. J. Pharmacol.* 1998, *359*, 33-40).

Sexual dysfunction

In vivo experiments have shown that a 5-HT_{2C} receptor agonist elicits penile erections in the rat and that this effect is inhibited by the 5-$HT_{2C/2B}$ receptor antagonist SB-206553, but not mimicked by the somewhat selective 5-HT_{2B} receptor agonist BW-723C86 (Millan et al. "5-HT_{2C} receptors mediate penile erections in rats: actions of novel and selective agonists and antagonists." *Eur. J. Pharmacol.* 1997, *325*, 9-12).

Memory disorder (e.g., Alzheimers disease)

Arjona et al. ("Effect of a 5-HT(2C) serotonin agonist, dexnorfenfluramine, on amyloid recursor protein metabolism in guinea pigs. *Brain. Res.* **2002**, *951*, 135-140) describe studies that "indicate that the pharmacological activation of 5-HT_{2C} receptors can stimulated CSF APP secretion and reduce Aβ production in vivo." Arjona et al. conclude that "5-HT_{2C} receptors, which apparently are localized to the brain, may represent useful targets for the development of treatments for Alzheimer's disease.

Thus, the foregoing indicates that there is an established link between 5-HT_{2C} modulation and the disorders and conditions recited in claims 13-21 as presently amended. Applicants therefore respectfully request that the rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1 and 4-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Baroni et al., EP 0 580 465 (Baroni). The Office has argued (Office Action, pages 16-17, emphasis added):

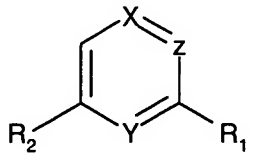
> Marcoss et al. [*sic.*, Baroni] teaches several heterocyclylpiperazine compounds useful as %-HT3 agonists, which include the instant compounds. See entire documents, especially page, formula I and note the definition of X, Y, R, R_1 and R_2 overlap with instant variable groups. Note when R_2 is halogen, the compounds taught by Baroni et al. include instant compounds. ...
>
> Instant claims require a pyrimidine core while Baroni et al exemplifies only pyridine core. **However, Baroni et al clearly teaches equivalency of the exemplified pyridine compounds with those of pyrimidine compounds generically claimed for compound of formula I.** See page 2 and note Y can be N and with X as CH.
>
> Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted piperazinyl-pyrimidines including those generically taught as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outlined above.

The rejection of claims 11, 12, 23, and 24 are moot in view of their cancellation.

Applicants respectfully disagree.

The Claimed Compounds

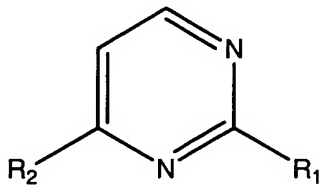
The inventors have discovered that compounds of formula I (which include compounds having pyrazine, pyrimidine, and pyridine cores) are capable of modulating the 5-HT_{2c} receptor.



(I)

As such, these compounds are useful for the treatment of 5-HT_{2c} receptor-related conditions and disorders (e.g., eating disorders; obesity; memory disorders; mood disorders; anxiety disorders; sexual dysfunctions, epilepsy, or urinary disorders; pain; substance abuse; and schizophrenia).

The present claims are directed to various 2,4-disubstituted pyrimidinyl compounds having general formula (**A**):

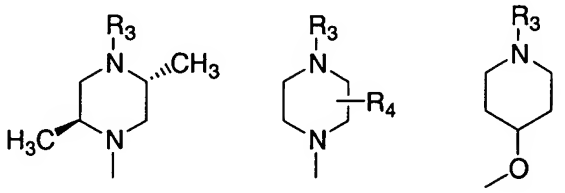


(**A**)

and to methods of making and using these compounds.

Substituents R_1 and R_2 are defined in claim 1 as follows (emphasis added):

"R_1 and R_2 are each, independently, selected from a **group A** consisting of:



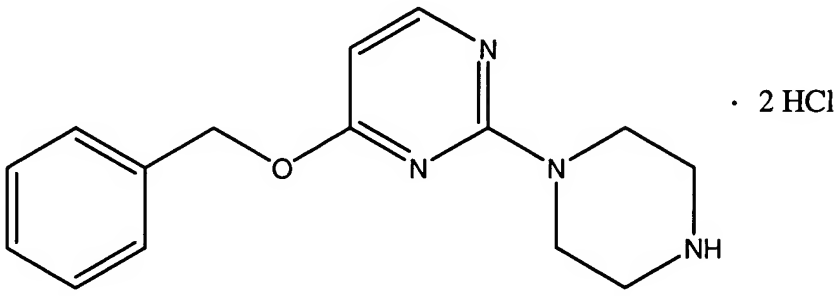
or from a **group B**, consisting of aryl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkoxy, aryloxy-C_2-C_6-alkoxy, heteroaryloxy-C_2-C_6-alkoxy, 1-indanyloxy, 2-indanyloxy, aryloxy, heteroaryloxy, arylthio, heteroarylthio, C_5-C_6-cycloalkylthio, C_5-C_8-alkoxy, C_5-C_8-alkylthio, C_3-C_6-alkynyloxy, C_3-C_6-alkenyloxy, fluoro-C_2-C_4-alkoxy, C_4-C_8-cycloalkyloxy, C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, halogen, aryl-C_1-C_4-alkylthio, heteroaryl-C_1-C_4-alkylthio, aryl-C_1-C_4-alkylamino, heteroaryl-C_1-C_4-alkylamino, heteroaryl and aryl;"

As mentioned previously, the claims further requires, *inter alia*, that (i) R_1 and R_2 must be different from one another; and (ii) R_1 and R_2 cannot both be selected from group A or from group B (i.e., one of R_1 and R_2 must be selected from group A, and the other must be selected from group B).

There are over 100 compounds exemplified in the present Specification. More specifically, Applicants have synthesized and tested formula (I) compounds having pyrazine, pyrimidine, and pyridine cores (see Examples 1-124 and subsequent section on pharmacological testing). The Specification states as follows with regard to the 5-HT_{2c} receptor affinity of their exemplified compounds (Specification at page 84, lines 1-8):

> The 5-HT_{2c} receptor affinity of compounds in the Examples was determined in competition experiments, where the ability of each compound in serial dilution to displace ^{3}H-labelled 5-HT, bound to membranes prepared from a transfected HEK293 cell line stably expressing the human 5-HT_{2c} receptor protein, was monitored by Scintillation Proximity Assay technology. Non-specific binding was defined using 5 μM mianserin. Results obtained for exemplary compounds of the invention are illustrated in Table 1 below. Typically, the 5-HT_{2C} receptor affinity values (K_i, nM) were in the range of 1 nM to 1500 nM.

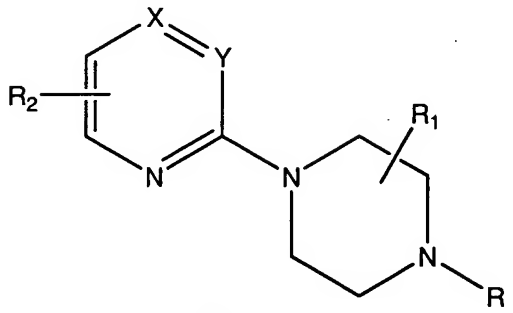
In particular, the pyrimidinyl compound of Example 32, 4-(Benzyloxy)-2-(1-piperazinyl)pyrimidine dihydrochloride, exhibited a Ki of 48 nM. The chemical structure of this compound is shown below.



· 2 HCl

Baroni

Baroni discloses a genus of compounds having formula (**B-1**), which are described as being 5-HT_3 agonists:



(B-1)

in which,

R is H or C_1-C_4 alkyl;

R_1 is H of CH_3;

R_2 is H or halogen;

Each of X and Y is -CH=, or one of X and Y is -CH=, and the other is -N=.

There are only three compounds exemplified in Baoni, all of which are compounds having a **pyridyl** core ring (i.e., each of X and Y is -CH=). There is no indication that Baroni made or tested any compounds having a pyrimidinyl core ring.

Legal Standards for Obviousness

The Federal Circuit in *In re Kotzab* 55 USPQ2d 1313, 1316 (2000) discussed the requirements for establishing a *prima facie* case of obviousness where the obviousness rejection is based on a **single** prior art reference (as is the case with the present rejection) (emphasis added):

> Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582, 37 USPQ2d 1314, 1318 (Fed. Cir. 1996).

The Federal Circuit in *Kotzab* also held that a showing of suggestion or motivation in the prior art must be supported by evidentiary findings of fact, and that broad conclusory statements do not constitute such evidence of a showing of suggestion or motivation (*In re Kotzab* 55 USPQ2d at 1317):

> Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. Broad conclusory statements standing alone are not 'evidence.'

Applicants' Rebuttal

The Office has concluded that the present claims are obvious over the teachings of the single reference Baroni (Office Action, pages 16-17):

> Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted piperazinyl-pyrimidines including those generically taught as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outlined above.

The Office has argued that a person of ordinary skill in the art would have been motivated by Baroni to prepare the claimed compounds because "Baroni et al clearly teaches **equivalency** of the exemplified pyridine compounds with those of pyrimidine compounds generically claimed for compound of formula I" (Office Action, page 16).

As discussed above, the Office "must" provide "particular findings" related to its showing of a motivation to modify the teachings of the prior art (see above discussion regarding *In re Kotzab*). There is no express or implicit teaching in Baroni of any equivalence between Baroni's exemplified pyridine compounds and Baroni's non-exemplified and generically claimed pyrimidine compounds. The Office's assertion that these two classes of compounds are equivalent is based only on the observation that pyrimidines fall within the Baroni genus. As mentioned elsewhere, there is no indication that Baroni even made or tested any compounds having a pyrimidinyl core ring, much less conducted comparative experiments to determine whether compounds having a pyridyl core and compounds having a pyrimidinyl were equivalent

in any way. The Office's assertion of "equivalency teaching" in Baroni is but a broad conclusory statement that is based solely on the observation (and not particular findings of fact) that pyrimidine compounds are "generically taught" by Baroni. Applicants submit that the Office has not met its burden to provide "particular findings" related to its showing of a motivation to modify the teachings of Baroni to arrive at the claimed compounds.

In any event, **the fact that a claimed compound or subgenus is encompassed by a prior art genus is not in and of itself sufficient to create a *prima facie* case of obviousness.** As the Federal Circuit explained in *In re Baird* 29 USPQ2d 1550, 1552 (1994):

> The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (rejecting Commissioner's argument that 'regardless [] how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it') *Baird* at 1552.

The Federal Circuit in *Baird* accorded appreciable weight to the structural nature of the "typical," "preferred," and "optimum" compounds of the prior art reference in determining whether the prior art reference taught or fairly suggested the claimed compounds. As discussed elsewhere, there are only three compounds exemplified in Baoni, all of which are compounds having a **pyridyl** core ring (i.e., each of X and Y is -CH=), and not a pyrimidinyl core ring. In addition, most of the substituents contemplated for R_1 and R_2 in Applicants' claim 1 do not overlap with the corresponding substituents in Baroni and are not suggested by Baroni. In short, the Office has effectively said no more than some of Applicants fall within Baroni's genus, but this in and of itself is insufficient to establish the Office's *prima facie* case.

In summary, "[A] reference must be considered not only for what it expressly teaches, but also for what it fairly suggests." *In re Baird* 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Baroni does not teach or fairly suggest any evidence pointing to the equivalence between his exemplified pyridyl compounds and his non-exemplified pyrimidinyl compounds. Applicants submit the motivation or suggestion to prepare the claimed compounds is found **only** in Applicants' Specification. For the reasons set forth above, the Office has failed to establish that

a person of ordinary skill in the art would have been motivated to make Applicants' claimed compounds or use them as 5-HT_{2c} receptor modulators. As such, the Office's *prima facie* case of obviousness is incomplete. Applicants therefore respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance.

Enclosed is a $1,020 check for the Three Month Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing attorney Docket No.: 13425-056002.

Respectfully submitted,

Date: May 9, 2006

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